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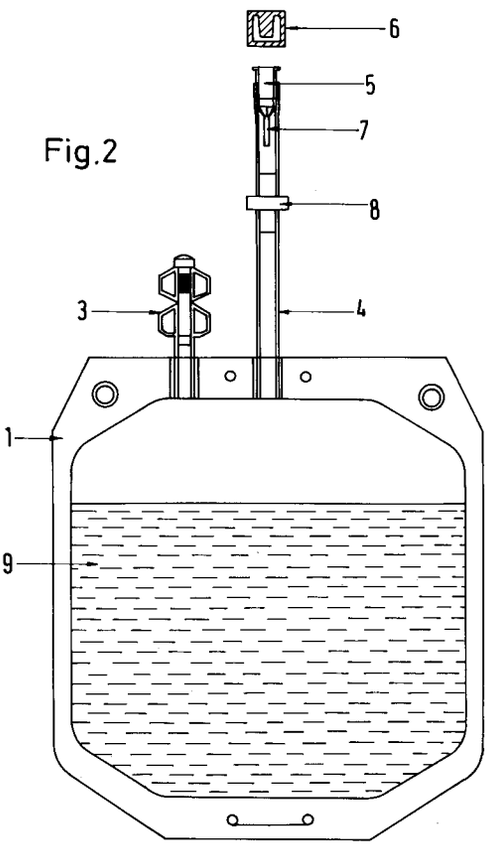
(54) Admixture container for connecting a syringe.

(57) A collapsible plastic IV container (1) is fitted with a sealable tube (4) which is provided with a female luer connector (5). A solution of a drug that is contained in a syringe can be diluted in the IV solution without the use of a needle, by direct coupling of the male luer connector (11) of the syringe to the female luer connector (5) on the container (1) with the IV solution. After the drug has been added, the tube (4) is sealed, producing a hermetically closed container (1) with the diluted, reconstituted drug solution. Use of this method and apparatus for the reconstitution or dilution of drugs increases the safety, by eliminating the use of needles and administration ports with rubber membranes and thereby reducing the chances of inadvertent exposure of hospital personnel to hazardous drugs.

Fig.2



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Our present invention relates to a method of diluting a drug-containing intravenous solution or for aseptically forming a solution of a drug for intravenous administration and to an apparatus utilizing this method. More particularly, the invention relates to the preparation of intravenous administration solutions without the need for needles for injecting a drug into the liquid vehicle or diluent solution.

Many drugs require reconstitution and/or dilution in an IV (intravenous) solution before they can be administered to patients. These drugs are generally life-saving medicaments that need to be injected directly into the vein of the patient to get the desired pharmacological effect. Dilution in an infusion solution can for instance be necessary to acquire the needed pharmacokinetic profile (i.e. a constant steady state plasma level) or to reduce the potential toxic effect of the drug. This is specially true for cytotoxic drugs, most of which would cause serious damage to the vein if they would be injected without prior dilution.

Reconstitution of potent and hazardous drugs is preferably performed under direct supervision of the hospital pharmacy. After reconstitution in the pharmacy these solutions are administered to the patient.

The drugs which must be diluted are generally supplied either in a glass vial with a rubber stopper or in a glass ampoule. They may either be supplied as a dry powder or they may be supplied in a concentrated solution. These drugs derive from many different suppliers and may vary in size, color, dosage, quality, additives, etc.

The most common intravenous solutions that are used for the reconstitution or dilution of drugs are 5% dextrose and 0.9% sodium chloride solutions, the latter generally being referred to as physiological saline.

These intravenous solutions may be packaged in rigid containers such as glass bottles, in semi-rigid containers made of a plastic, e.g. polypropylene, or in flexible collapsible containers made of e.g. polyvinylchloride (PVC).

The state of the art in preparing a powdered drug in an intravenous form is to first inject a portion of the diluent into the drug vial. Since the powdered form of the medicament may be in lyophilized form, this step is referred to as a reconstitution.

The diluent for this reconstitution may be taken from the IV container in which the final dilution will take place or may be taken from a different IV container or from an ampoule.

First, the syringe is filled with the diluent. Then, the needle of the syringe is pierced through the rubber stopper of the drug vial and the diluent is introduced into the vial through the syringe.

The requirements that syringes, needles and luer connectors must comply with are governed in many standards, especially ISO. These standards describe, for example, the specifications for the luer connectors that are fitted on the needle and on the syringe and therefore guarantee a perfect, leak-tight match of the male and female connectors.

Generally, needles - those used for reconstitution as well as those used for the injection of fluids into the patient's body - are fitted with a female luer connector. Syringes, therefore, are usually fitted with a male luer or luer-lock connector. For critical tasks, usually the luer-lock connector is preferred. There are several patents for luer connectors; see for instance United States Patent 4,639,019 and United States Patent 4,452,473.

After mixing and dissolution of the powder in the vial, the solution is drawn back into the syringe and may be injected by the syringe through an additive port in the container in which the intravenous medium has been packaged.

For pharmaceuticals packaged in ampoules, reconstitution is generally not required as these drugs are delivered in a solution. After breaking of the neck of the ampoule, the solution can be drawn directly into the syringe and can subsequently be introduced into the intravenous solution via the additive port in the container.

Depending on the dose needed by the patient for the desired pharmacological effect, part of the contents of the vial, the entire contents of the vial, or more than one vial may be needed. Sometimes the container with the IV solution must be punctured more than once to introduce the needed dose into the container.

Glass bottles and semi-rigid containers usually have only one port, consisting of a rubber stopper. Flexible containers, as produced by Abbott, Baxter and McGaw in the US or NPBI in the Netherlands may nave two ports. One of these ports is intended for the addition of drugs to the IV solution. These ports usually comprise a rubber membrane separated from the IV solution by a PVC membrane. The PVC membrane protects the solution against components that may leach from the rubber and that can contaminate the solution. Furthermore, the PVC membrane will protect the solution against particles that can be released by the rubber. These rubber membranes should preferably be punctured only once. If the membrane is accidentally punctured at the same place more than once, there is a highly increased chance of leakage at that place. Therefore, manufacturers usually advise against piercing the rubber membrane more than once unless absolutely necessary.

The diameter of the lumen of the needle chosen for reconstitution of drugs is a compromise. The needle should neither be too small nor too

large. The smaller the needle, the more force is needed by the person doing the reconstitution as the needle is the part with the smallest diameter in this system and presents the main constriction.

However, the larger the diameter of the needle, the larger the damage to the rubber membrane will be. With a larger needle, also the chance of coring of the rubber membrane is increased.

Rubber particles in the reconstituted IV solution are, however not acceptable from a medical point of view. In conclusion, a larger needle is more convenient and requires less force to do the reconstitution, but at the same time increases the chances of subsequent leakage of the port of the IV container and of rubber particles in the solution.

After reconstitution or dilution, the container is inspected for particulate matter and leakage. If the container leaks, it will be discarded. After labelling and packaging, it is transported to the ward. There, after inspection and after introduction of an administration set, the reconstituted solution is administered to the patient.

Several hazards are associated with the dilution or reconstitution of drugs. They derive mainly from the fact that some drugs are extremely toxic, even in low doses if exposure takes place over a period of time. This is especially true for the cytotoxic drugs that are used to treat cancer. Most of these are themselves carcinogenic. For that reason, several precautions have been implemented in the hospitals to prevent inadvertent exposure of personnel to these drugs. Of special concern are spillage, leakage and aerosols.

To prevent inadvertent exposure, most hospitals follow strict procedures which are based on guidelines issued by e.g. the American Society of Hospital Pharmacists or which are based on local rules or regulations. Generally, they comprise working in a special (down-flow) cabinet with filtered air, wearing special protective clothing an special rules for handling of the product and of the waste that is generated during reconstitution.

Spillage, leakage and aerosols may occur during reconstitution, during transport to the ward, during administration to the patient and through waste. During the process of reconstitution of the drug, of special concern is the addition of the drug to the infusion solution as this is performed with a needle. This needle cuts through the rubber and PVC membranes of the port of the container. Upon removal of this needle from the container, there is generally some leakage. This is due to the fact that closure of the rubber membrane is not based on a chemical process, but is purely a physical process. Therefore, upon removal of the needle, small capillaries will remain in the membrane at the place where the needle has cut through the material.

These capillaries usually contain some fluid, which may contain the drug solution, originating from the outside of the needle. The small capillaries may leak some of this fluid, especially when the pressure in the container is increased due to the volume of drug solution that was added to the IV container. This increased pressure may also lead to the production of aerosols.

It is, however, important to realize that the ruptured membrane with the cut rubber will remain on the bag and may not only cause leakage of the bag during reconstitution, but also during transport or on the ward during administration of the drug.

The use of a needle for the addition of a drug to an IV solution in a flexible bag may also lead to accidental rupture of the bag, which is especially dangerous as the total dose of the medicament may be spilled in the LAF-cabinet.

Another disadvantage associated with the use of needles is the small diameter of the lumen and subsequently the force needed during reconstitution of the drugs. Especially when large volumes of fluid have to be injected, the use of needles is very tiresome for the operator.

Finally, another disadvantage of this method is that the PVC membrane is punctured during reconstitution, leaving a direct contact between the rubber and the solution. The solution may be contaminated by leakage of components from the rubber and alternatively, the rubber may absorb the drug or other components from the solution.

Several systems have been developed to improve the reconstitution process of drugs in an IV solution. For example, several types of double-pointed needles, commonly referred to as transfer needles have been developed. This needle, and the reconstitution process with this needle are described in e.g. U.S. Patent 4,759,756.

In U.S. Patent 4,614,267, a dedicated system is described in which a dedicated vial containing a drug, can be screwed into a container with the IV solution.

In U.S. Patent 4,997,430 an apparatus and connector are described for direct coupling of a medicament in a drug vial to an IV solution in a container.

These systems however, are not generally applicable. They allow for the reconstitution of the contents of one vial with the drug in the contents of one container with IV solution. Therefore, with these systems, only fixed doses and fixed concentrations of diluted drugs can be made.

However, many, especially cytotoxic, drugs require dosing based on the patient's weight and/or skin surface. For that purpose, a flexible reconstitution system is required where the dose and concentration of the drug can be easily adjusted to the patient's needs while at the same time reducing the changes of spillage, leakage and aerosols.

It is an object of the present invention to provide an improved method and apparatus for the reconstitution of flexible doses of drugs in IV solutions in which many of the drawbacks of the method or reconstitution as mentioned above, are avoided.

More specifically, an object of this invention is to provide a method and apparatus for this reconstitution procedure without the use of needles and rubber administration ports.

These objects and others which will be apparent hereinafter are attained, in accordance with the invention in a method of aseptically forming a solution of a drug for intravenous administration which comprises the steps of:

providing a collapsible plastic container with a sterile intravenously administrable liquid and a female luer connector attached to the container by a sealable tube;

connecting a syringe containing a solution of an intravenously administrable drug with the tube by joining a male luer connector with the female luer connector;

injecting the solution into the liquid through the tube by displacing the solution from the syringe while the male luer connector is joined with the female luer connector; and

thereafter sealing the tube.

In apparatus terms, the invention comprises:

a collapsible plastic container containing a sterile intravenously administrable liquid;

a sealable tube connected with said container; and

a female luer connector on said tube and directly connectable with a syringe containing a solution of an intravenously administrable drug by the joining of a male luer connector of said syringe with said female luer connector.

The assembly of the syringe containing the drug solution and having a male luer connection connected to the female luer connection of the container is also part of the invention.

According to a feature of the invention, the sealing of the tube involves cutting the seal into two parts, thereby sealing off the tube and disconnecting the syringe from the container.

A break-away connector can be provided in a path of the solution between the syringe and the container by integrating it into the female luer connector, providing it along the tube between the female luer connector and the container or providing it at a junction of the tube with the container.

A clamp can be provided on the tube to shut-off flow therethrough. Alternatively or, in addition, a one way check valve can be fitted into the tube to permit flow only toward the container. A cap on the female luer connector can prevent accidental touch contamination thereof.

The invention, therefore, utilizes a collapsible plastic container, containing an IV solution, to which is attached a female luer or luer-lock connector via a sealable tubing. The luer connector allows for direct coupling of the male luer connector of the syringe containing the dissoluted medicament to the IV container and thus eliminating the use of a needle for introduction of the drug into the infusion solution. After introduction of the drug in the container, the tube is sealed, producing a hermetically closed reconstituted IV solution.

The above and other objects, features and advantages of our invention will become more readily apparent from the following description, reference being made to the accompanying highly diagrammatic drawing in which:

FIG. 1 is a diagrammatic elevational view of an intravenous bag fitted with a female luer connector and showing the cap removed therefrom;

FIG. 2 is a view similar to FIG. 1 illustrating another embodiment of the invention;

FIG. 3 is still another view of an intravenous bag embodying the invention;

FIG. 4 is a diagram illustrating the sealing of the tube according to the invention;

FIG. 5 is an elevational view showing the sealed tube;

FIG. 6 is a view illustrating the positioning of the break-away connector at the junction between the tube and the intravenous bag;

FIG. 7 shows the break-away connector within the tube and illustrates the tube in cross section;

FIG. 8 is a perspective view showing a pinch clamp for use with the tube of FIGS. 1 - 3; and

FIG. 9 is an elevational view of a portion of the assembly of any of FIGS. 1 - 3 illustrating the syringe attached thereto.

FIG. 1 shows an IV bag fitted with three ports. One port is provided with a filling tube 2, used by the manufacturer to fill the bag with the IV solution 9. This filling tube is sealed after filling. A second port is provided with an administration port 3. The port in this specific drawing is a 'twist-off' administration port. This port can, however, be of any known configuration and is not limited to this special construction. The plug of this port in the drawing can be removed by turning the upper set of side-wings and taking the plug out.

After removal of the plug, the port can be used to connect an administration set to the IV bag. Via this port, the reconstituted and diluted drug solution can be administered to the patient.

The third port is provided with a piece of tubing 4, fitted with a female luer connector 5 with a cap 6 and a break-away connector 7. The tube 4 is made from a sealable plastic material, for example PVC or polyethylene. The length of the tubing should allow for sealing, being at least 2 cm but

preferably being as short as possible to keep the dead volume in the tube as small as possible and to prevent packaging problems.

The female liner connector 5 must comply with ISO and/or local standards to allow for a leaktight fit with a male liner or luer-lock connector from a syringe. The female luer connector 5 is fitted with a cap 6 to protect the connector 5 against accidental touch-contamination during use. In this embodiment, the liner connector 5 is integrated with a break-away connector 7 as a means to shut off the tube. However, the break-away connector 7 may be located anywhere in the fluid path and is not necessarily integrated with the female luer connector.

For example, in FIG. 6 we show the break-away connector 7 received in the tube 4' at the junction with the IV bag 1'. Alternatively, the break-away connector 7'' may be located within the tube 4'' between the female liner connector 5 and the bag 1. The break-away connector in each case prevents the liquid in the bag from escaping through the liner connector prior to receiving the drug. It may have a sleeve 7^{IV}, bonded to the tube or forming part of the luer connector, and a pin 7''' which, when broken off, opens the break-away connector. This pin can be broken off by flexing the tube or the like.

As can be seen from FIG. 4, the tube 4 can be pinched-off at 4a by a heat sealing operation to effect the sealing of the tube after the syringe has been introduced and the heat seal 4a can be cut in half along the line 4b to form the sealed end 4c of the tube 4.

For some applications, the presence of a one-way check valve 8 in the tube between the container 1 and the liner connector 5 may be desirable. This valve 8 should block leakage from the container, while allowing the addition of fluids to the container. The valve can, for example, prevent leakage from the tubing when the syringe is disconnected from the IV bag. This could be necessary if the contents of more than one syringe must be added to the IV container. For the same purpose, also a slide clamp 10 (FIG. 8) could be used to shut off the tube temporarily.

FIG. 2 shows an IV bag fitted with two ports. One port is provided with an administration port as in FIG. 1 while the second port is provided with the tubing with the female liner and break-away connector. The bag can be filled with IV fluid either through the first port and be closed with the twist-off or through the second port and be closed with the liner connector during production.

Fig. 3 shows an intravenous container with only one port. During production, the bag is filled with IV fluid through the tube. After filling, the tube is fitted with the liner connector. Administration of the reconstituted drug solution to the patient can be accomplished by connecting an administration set to the tube of the bag by means of sterile docking, after the drug has been reconstituted and the tube has been sealed. Methods for making sterile connections have been described in several patents. An apparatus for sterile connections is marketed in the United States by the Haemonetics Company.

Generally, any combination of ports on the bag is permissible as long as the necessary functions of filling, reconstitution, and administration of the fluid can be carried out.

If the medicament is a dry powder, first it is dissolved as described above by introducing a volume of diluent into the drug container or drug vial with the aid of a syringe and a needle.

This diluent can be taken from any IV container or from an ampoule. Also, the diluent can be taken from the container of this invention by connecting a syringe to the liner connector, breaking the break-away connector and taking the fluid from the container. Before disconnecting the syringe, the tube can be shut off temporarily with a clamp.

After dissolution, the drug solution is drawn into the syringe, if necessary with the aid of a needle. Then, the syringe is coupled directly with its male luer connector to the female liner connector of the IV container. The needle is discarded. After breaking of the break-away connector the solution of the drug is introduced into the infusion solution and thoroughly mixed.

After mixing, the tube is sealed. Depending on the material of the tube, one of several techniques can be chosen for sealing the tube, for example heat sealing or RF welding. This sealing can be done with a standard apparatus such as marketed by the Sebra Company in the United States.

The seal can then be cut in the middle. Part of the original tube remains attached to the infusion container with the reconstituted solution, while the other part stays attached to the female luer and the syringe. After cutting the seal in two halves, both ends are closed. The part with the syringe can be discarded.

For dissolved drugs in ampoules or vials, the same method can be used for reconstitution without the dissolution step.

In an alternative, the tubing is not sealed. The syringe remains firmly attached to the infusion container during transport to the ward and during administration of the IV solution to the patient.

If the tubing of the container is sealed after reconstitution and dilution, this tube can also be used for the administration of the fluid to the patient by connecting an administration set to that tube via a sterile connection technique, as already mentioned before. The administration set can be a standard set and may contain a drip-chamber etc., or may be a simple tube for piggy-backing the

solution on a standard IV administration set.

In comparison with the state-of-the-art technique employing a needle to introduce the drug into the IV solution, this method offers several advantages.

As the method allows for direct coupling of the syringe and the IV container, it is fast and convenient and safe. As no needles are used, less pressure is needed to inject the soluted drug in the IV container which allows for faster and easier reconstitution. Also, the containers can not be punctured accidentally, which happens frequently with flexible containers during reconstitution with needles. Needle pricks of personnel are eliminated.

Furthermore, there is no contact between the drug and a rubber membrane during any stage of the reconstitution, transportation or administration process. Therefore, the rubber cannot contaminate the solution and the rubber cannot absorb components from the solution.

Also, the IV solution cannot be contaminated with rubber particles due to coring of the membrane.

However, the major advantage of this method of working is that after reconstitution the female luer connector is sealed and therefore the container is again a hermetically closed system after reconstitution. Leakage and drops from the punctured membrane cannot occur. This is in striking contrast to the present method of working, in which the IV product is transported through the hospital and used on the ward with a punctured rubber membrane.

Use of this method of reconstitution therefore reduces the chances of leakage and aerosols generated by hazardous, reconstituted IV solutions in the hospital.

In FIG. 9 I have shown the assembly with the syringe as attached by its luer connector 11, namely, a male luer connector, to the female luer connector 5 of any of the bags of FIGS. 1 - 3. The solution from the syringe has, however, been injected into the bag in this illustration so that the body 12 of the syringe and its plunger 13 are also visible.

Claims

1. A method of aseptically forming a solution of a drug for intravenous administration, comprising the steps of:

   providing a collapsible plastic container with a sterile intravenously administrable liquid and a female liner or luer-lock connector attached to the container by a sealable tube;

   connecting a syringe containing a solution of an intravenously administrable drug with said tube by joining a male liner connector with said female luer or luer-lock connector;

   injecting said solution into said liquid through said tube by displacing said solution from said syringe while said male luer connector is joined with said female luer or luer-lock connector; and

   thereafter sealing said tube.

2. The method defined in claim 1 wherein said tube is formed with a seal between said syringe and said container, said method further comprising the step of cutting said seal into two parts, thereby sealing said tube and disconnecting said syringe from said container.

3. An apparatus for aseptic intravenous administration of a solution of a drug, comprising:

   a collapsible plastic container (1) containing a sterile intravenously administrable liquid;

   a sealable tube (4) connected with said container (1); and

   a female luer connector (5) on said tube (4) and directly connectable with a syringe containing a solution of an intravenously administrable drug by the joining of a male luer connector of said syringe with said female luer or luer-lock connector (5).

4. The apparatus defined in claim 3, further comprising a break-away connector (7) in a path of said solution between said syringe and said container (1).

5. The apparatus defined in claim 4 wherein said break-away connector (7) is integrated in said female luer or luer-lock connector (5).

6. The apparatus defined in claim 4 wherein said break-away connector (7) is provided along said tube (4) between said female luer or luer-lock connector (5) and said container (1).

7. The apparatus defined in claim 4 wherein said break-away connector (7) is provided at a junction of said tube (4) with said container (1).

8. The apparatus defined in claim 3, further comprising a clamp (10) on said tube (4) to shut off flow therethrough.

9. The apparatus defined in claim 3, further comprising a one-way checkvalve (8) in said tube (4) permitting only flow toward said container (1).

10. The apparatus defined in claim 3, further comprising a cap (6) on said female luer or luer-

lock connector (5) preventing accidental touch contamination thereof.

Fig.1

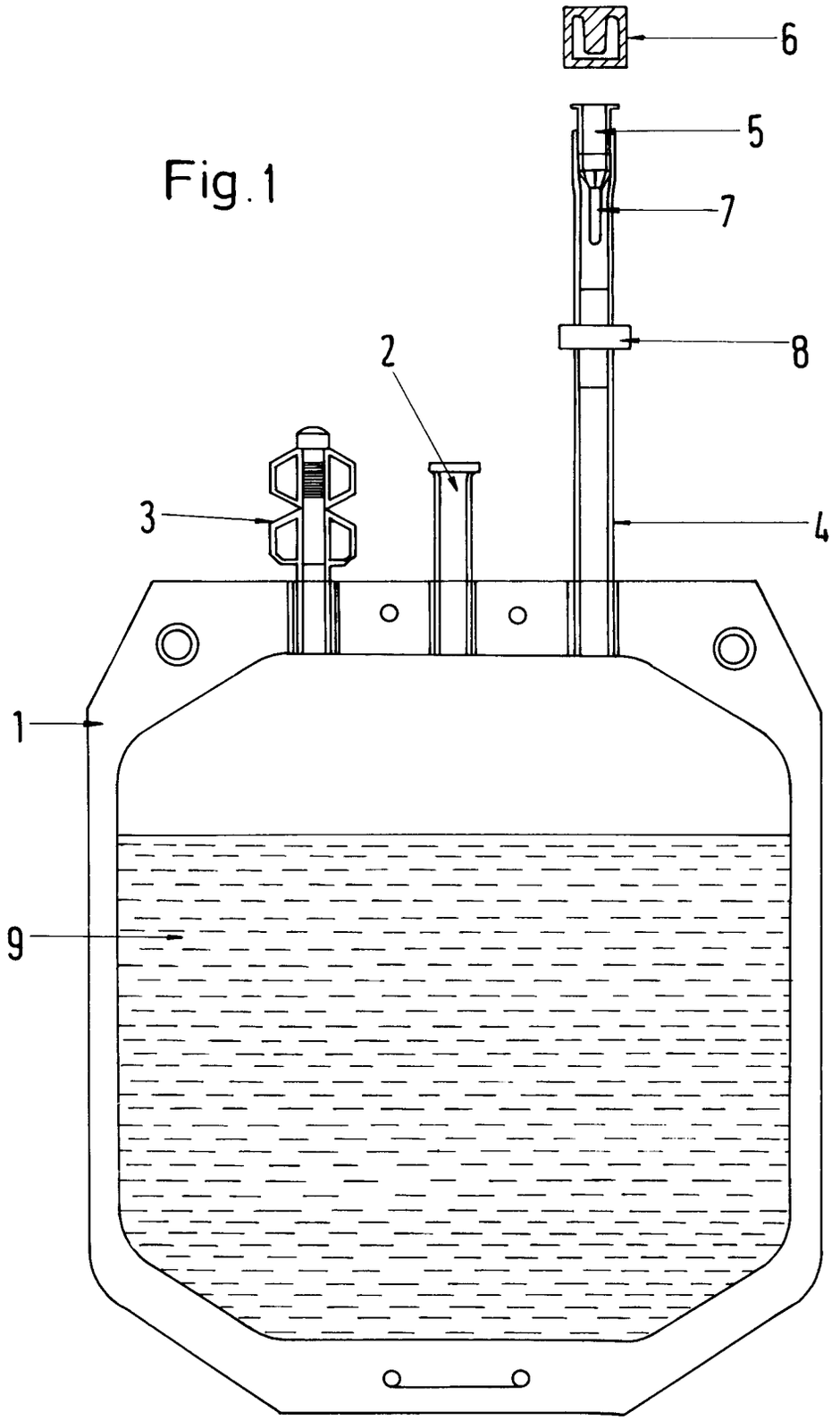


Fig.2

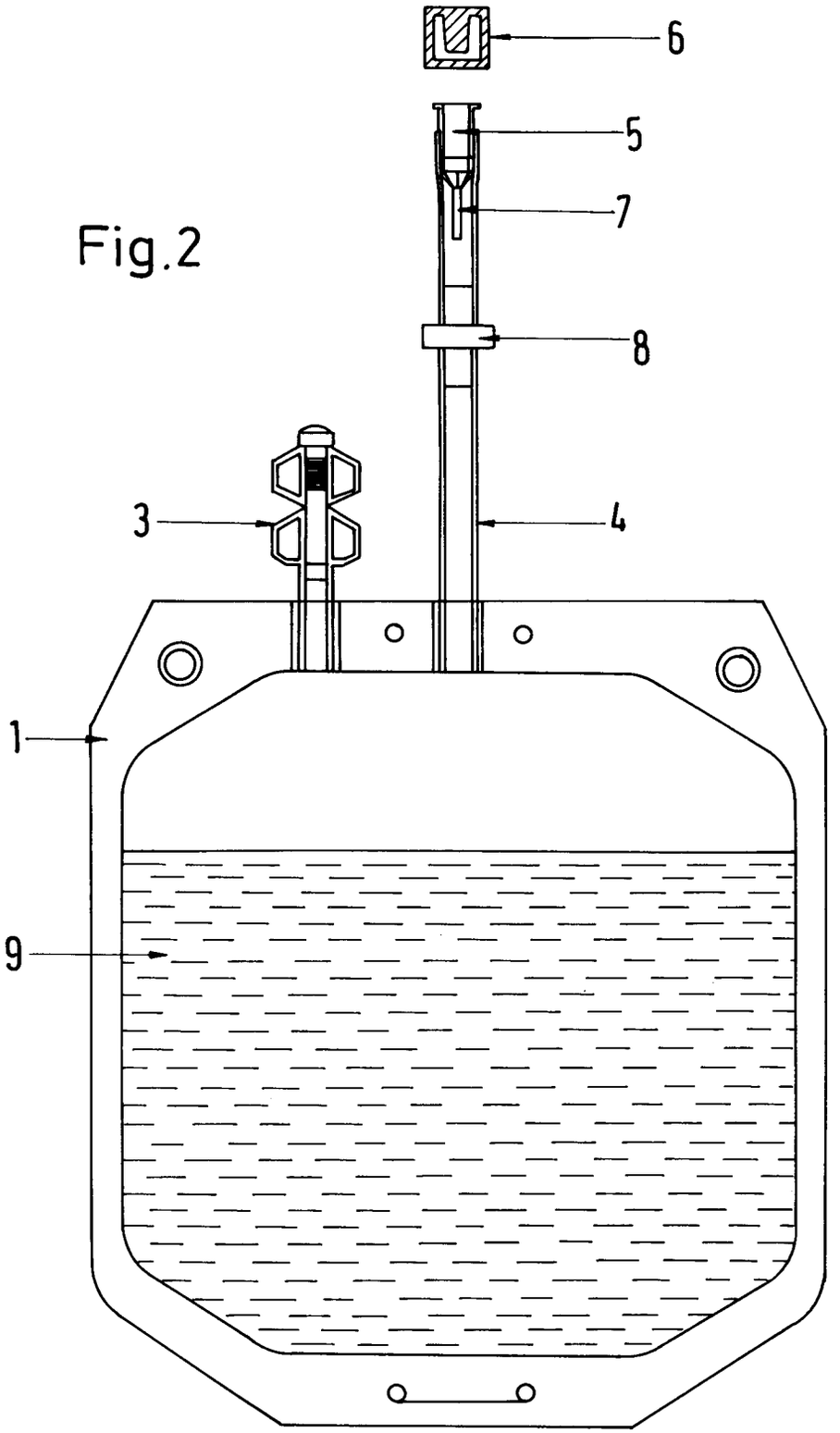


Fig.3

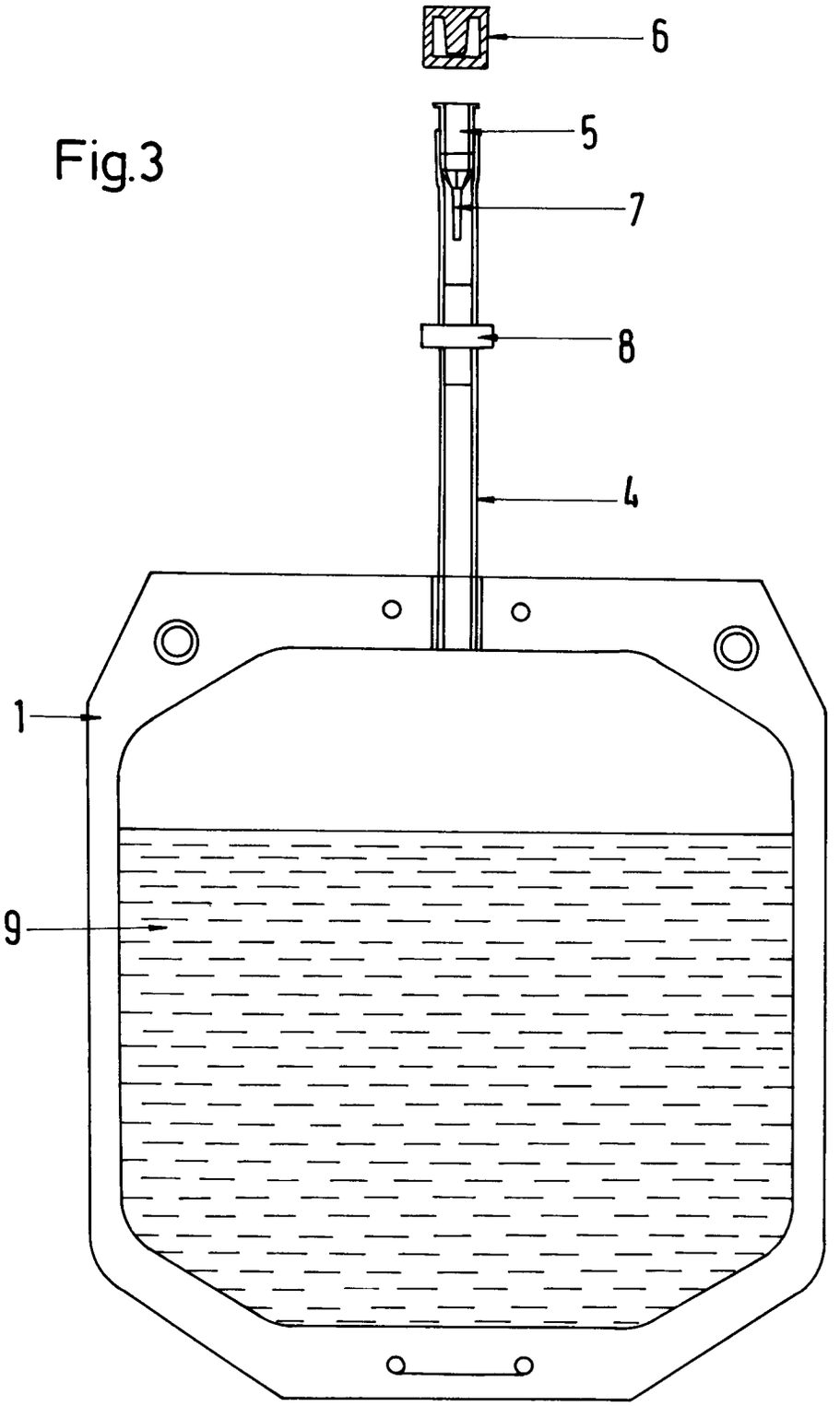


Fig.4

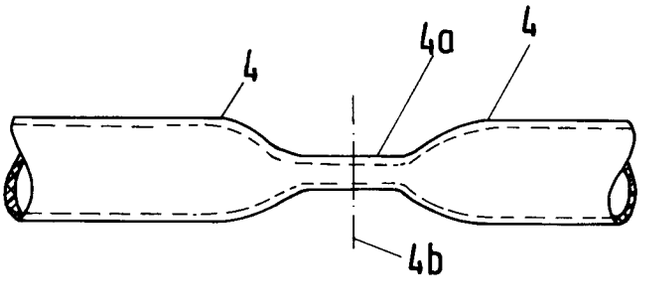


Fig.5

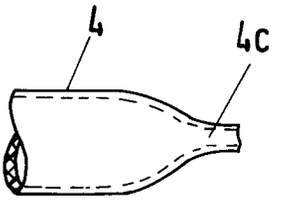


Fig.6

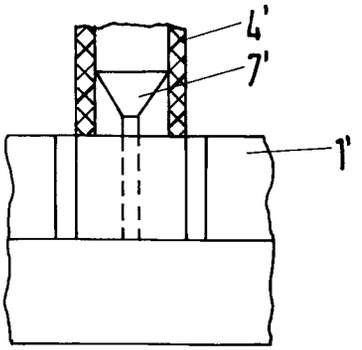


Fig.7

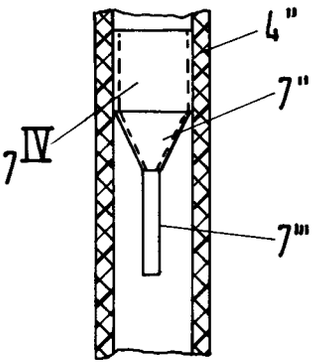


Fig.8

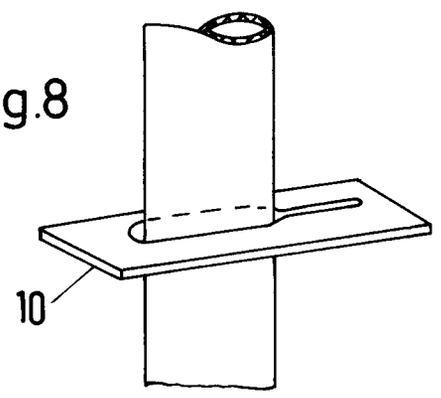
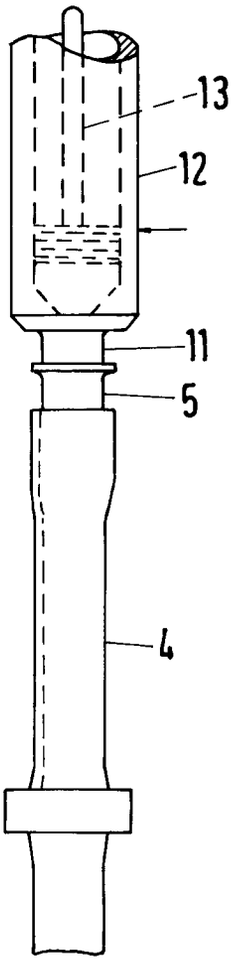


Fig.9



European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 5411

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	US-A-4 336 802 (STONE) * column 2, line 5 - line 36 * * column 3, line 4 - line 35 * * column 4, line 18 - line 25; figures 1-3 *	1,3,8	A61J1/10
X	CH-A-659 395 (SOLCO BASEL AG) * page 2, right column, line 9 - line 35; figure 1 *	1,3,8,10	
X	GB-A-1 428 373 (SMITH AND NEPHEW RESEARCH LTD) * page 2, line 57 - line 67 * * page 2, line 103 - line 106; figure 1 *	1	
A	GB-A-2 083 796 (BUCK) * page 3, line 60 - line 73; figure 4 *	2	
A,P	EP-A-0 469 515 (KAWASUMI LABORATORIES INC.) * column 4, line 23 - line 38; figure 2 *	4,6	
A	EP-A-0 175 274 (TERUMO KABUSHIKI KAISHA) * page 9, line 21 - page 10, line 11; figure 8 *	4,7	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A61J

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	28 JULY 1992	BAERT F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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